CASRN -- 7440-47-3

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Chromium(VI)
CASRN -- 7440-47-3
Last Revised -- 06/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Chromium(VI) >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. CAA REGULATORY DECISION

Action -- Intent to list under Section 112

Considers technological or economic feasibility? -- NO

Discussion -- Chromium VI is considered a human carcinogen (IARC Group I), and according to EPA's preliminary risk assessment from ambient air exposures, public health risks are significant. There is considerable uncertainty as to the carcinogenicity of other valence states of chromium and the proportion of chromium VI in emission or ambient air samples. The EPA indicated that it intends to add total chromium or chromium VI to the list of hazardous air pollutants for which it intends to establish emission standards under section 112(b)(1)(A) of the Clean Air Act. The EPA will decide whether to add total chromium or chromium VI to the list only after studying possible techniques that might be used to control emissions and further assessing the public health risks. The EPA will add total chromium or chromium VI to the list if emission standards are warranted.

Reference -- 50 FR 24317 (06/10/85)

EPA Contact -- Emissions Standards Division, OAQPS
(919)541-5571 / FTS 629-5571

---------<<< Chromium(VI) >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.12 mg/L [total chromium] (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- An MCLG of 0.12 mg/L for total chromium (Cr III and Cr VI) is proposed based on a provisional DWEL of 0.17 mg/L with data on human exposure factored in (0.10 mg/day in the diet and 0 mg/day by air). A DWEL of 0.17 mg/L was calculated from a NOAEL of 2.41 mg/kg/day in rats [1-year drinking water study (Cr VI)], with an uncertainty factor of 500 applied and consumption of 2 L of water/day assumed.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Kenneth Bailey / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< Chromium(VI) >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.05 mg/L [total chromium] (Interim, 1980)

Considers technological or economic feasibility? -- NO

Discussion --

Reference -- 45 FR 57332

EPA Contact -- Kenneth Bailey / Criteria and Standards Division, ODW / (202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

----------<<< Chromium(VI) >>>----------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 5.0E+1 ug/L

Fish Consumption Only -- None

Considers technological or economic feasibility? -- NO

Discussion --

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS (202)475-7315 / FTS 475-7315

<<< Chromium(VI) >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 1.6E+1 ug/L (1-hour average)
Chronic -- 1.1E+1 ug/L (4-day average)

Marine:

Acute -- 1.1E+3 ug/L (1-hour average)
Chronic -- 5.0E+1 ug/L (4-day average)

Considers technological or economic feasibility? -- NO

Discussion --

Reference -- 50 FR 30784 (07/28/85)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

----------<<< Chromium(VI) >>>----------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

----------<<< Chromium(VI) >>>----------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

----------<<< Chromium(VI) >>>----------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

----------<<< Chromium(VI) >>>----------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1 pound (Proposed, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The proposed RQ for chromium is based on potential carcinogenicity. Available epidemiological data on inhalation of hexavalent chromium indicate a hazard ranking of high based on a potency factor of 388.99/mg/kg/day and assignment to weight-of-evidence group A. This corresponds to an RQ of 1 pound.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Chromium(VI)
CASRN -- 7440-47-3

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Chromium(VI)
CASRN -- 7440-47-3
Last Revised -- 06/01/90

__VI.A. ORAL RfD REFERENCES

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Petrilli, F.L. and S. DeFlora. 1977. Toxicity and mutagencity of hexavalent chromium on Salmonella typhimurium. Appl. Environ. Microbiol. 33(4): 805-809.

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----------<<< Chromium(VI) >>>----------

__VI.B. INHALATION RfD REFERENCES

None

----------<<< Chromium(VI) >>>----------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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Fradkin, A., A. Janoff, B.P. Lane and M. Kuschner. 1975. In vitro transformation of BHK21 cells grown in the presence of calcium chromate. Cancer Res. 35: 1058-1063.

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----------<<< Chromium(VI) >>>----------

__VI.D. DRINKING WATER HA REFERENCES

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MacKenzie, R.D., R.U. Byerrum, C.F. Decker, C.A. Hoppert and R.F. Langham. 1958. Chronic toxicity studies. II. Hexavalent and trivalent chromium administered in drinking water to rats. Am. Med. Assoc. Arch. Ind. Health. 18: 232-234.

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SYNONYMS

Substance Name -- Chromium(VI)
CASRN -- 7440-47-3
Last Revised -- 03/31/87

7440-47-3
CHROMIC ION
CHROMIUM
CHROMIUM, ION
Chromium(VI)
CHROMIUM (VI) ION

Copper; CASRN 7440-50-8 (12/01/88)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Copper

File On-Line 09/07/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	no data	
Inhalation RfD Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	09/07/88
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENT FOR NONCARCINOGENIC EFFECTS

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Copper
CASRN -- 7440-50-8
Last Revised -- 09/07/88

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per mg/kg/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Copper >>>

Substance Name -- Copper
CASRN -- 7440-50-8
Preparation Date -- 09/01/87

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classified

Basis -- There are no human data, inadequate animal data from assays of copper compounds, and equivocal mutagenicity data.

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Copper >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Inadequate. Bionetics Research Labs (1968) studied the carcinogenicity of a copper-containing compound, copper hydroxyquinoline, in two strains of mice (B6C3F1 and B6AKF1). Groups of 18 male and 18 female 7-day-old mice were administered 1000 mg copper hydroxyquinoline/kg bw (180.6 mg Cu/kg) suspended in 0.5% gelatin daily until they were 28 days old, after which they were administered 2800 ppm (505.6 ppm Cu) in the feed for 50 additional weeks. No statistically significant increases in tumor incidence were observed in the treated 78-week-old animals.

In the same study, Bionetics Research Labs (1968) administered a single subcutaneous injection of gelatin (control) or 1000 mg of copper hydroxyquinoline/kg bw (180.6 mg Cu/kg) suspended in 0.5% gelatin to groups of 28-day-old mice of both strains. After 50 days of observation, the male B6C3F1 had an increased incidence of reticulum cell sarcomas compared with controls. No tumors were observed in the treated male B6AKF1 mice, and a low incidence of reticulum cell sarcomas was observed in the treated female mice of both strains.

Gilman (1962) administered intramuscular injections containing 20 mg of cupric oxide (16 mg Cu), cupric sulfide (13.3 mg Cu), and cuprous sulfide (16 mg Cu) into the left and right thighs of 2- to 3-month-old Wistar rats. After 20 months of observations, no injection-site tumors were observed in any animals, but other tumors were observed at very low incidence in the animals receiving cupric sulfide (2/30) and cuprous sulfide (1/30). As the relevance of the organic copper compound to the observation of sarcoma induction is uncertain and the incidence of tumors in rats treated i.m. with inorganic copper was very low, data are considered inadequate for classification.

<<< Copper >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Moriya et al. (1983) reported no increase in mutations in E. coli and S. typhimurium strains TA98, TA1535, TA1537 and TA1538 incubated with up to 5 mg copper quinolinolate/plate and in S. typhimurium TA98 and TA100 incubated with up to 5 mg copper sulfate/plate. Demerec et al. (1951) reported dose-related mutagenic effects in E. coli with 2 to 10 ppm copper sulfate in a reverse mutation assay. Negative results were obtained with copper sulfate or copper chloride in assays using S. cerevisiae (Singh, 1983) and Bacillus subtilis (Nishioka, 1975, Matsui, 1980, Kanematsu et al., 1980). Errors in DNA synthesis from poly(c)templates have been induced in viruses incubated with copper chloride or copper acetate (Sirover and Loeb, 1976). Chromosomal aberrations were induced in isolated rat hepatocytes when incubated with copper sulfate (Sina et al., 1983). Casto et al. (1979) showed enhanced cell transformation in Syrian hamster embryo cells infected with simian adenovirus with the addition of cuprous sulfide and copper sulfate. High concentrations of copper compounds have been reported to induce mitosis in rat ascites cells and recessive lethals in Drosophila melanogaster. Law (1983) reported increases in the percent lethals observed in Drosophila larvae and eggs when exposed to copper by microinjection (0.1% copper sulfate) or immersion (concentrated aqueous copper sulfate), respectively.

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT) <<< Copper >>>

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Copper. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. ECAO-CIN 417.

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Moriya, M., T. Ohta, K. Watanabe, T. Miyazawa, K. Kato and Y. Shirasu. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat. Res. 116(3-4): 185-216.

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Sirover, M.A. and L.A. Loeb. 1976. Infidelity of DNA synthesis in vitro: Screening for potential metal mutagens or carcinogens. Science. 194: 1434-1436.

<<< Copper >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The values in the 1987 Drinking Water Criteria Document for Copper have received peer and administrative review.

Agency Work Group Review: 09/15/87

Verification Date: 09/15/87

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

David J. Reisman / ORD -- (513)569-7588 / FTS 684-7588

W. Bruce Peirano / ORD -- (513)569-7540 / FTS 684-7540

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

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_V. SUPPLEMENTARY DATA

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

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_VI. REFERENCES

Substance Name -- Copper
CASRN -- 7440-50-8

Not available at this time

SYNONYMS

7440-50-8
Copper

Cyanide, free; CASRN 57-12-5 (03/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Cyanide, free

File On-Line 01/31/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	03/01/88
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	03/01/91
Drinking Water Health Advisories (III.A.)	on-line	08/01/90
U.S. EPA Regulatory Actions (IV.)	on-line	08/01/90
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Cyanide, free
CASRN -- 57-12-5
Last Revised -- 03/01/88

The Reference Dose (RfD) is based on the assumption that thresholds exist for

certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Cyanide, free >>>

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Rat Chronic Oral Study Howard and Hanzal, 1955	NOAEL: 10.8 mg/kg/day cyanide	100	5	2E-2 mg/kg/day
Weight loss, thyroid effects and myelin degeneration Rat Subchronic to Chronic Oral Bioassay Philbrick et al., 1979	LOAEL: 30 mg/kg/day cyanide			

*Conversion Factors: none

<<< Cyanide, free >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Howard, J.W. and R.F. Hanzal. 1955. Chronic toxicity to rats of food treated with hydrogen cyanide. J. Agric. Food Chem. 3: 325-329.

Philbrick, D.J., J.B. Hopkins, D.C. Hill, J.C. Alexander and R.G. Thomson. 1979. Effects of prolonged cyanide and thiocyanate feeding in rats. J. Toxicol. Environ. Health. 5: 579-592.

Hydrogen cyanide (HCN) is soluble in water and dilute acid (which includes the gastric environment) and is readily hydrolyzed to 1 molar equivalent of cyanide (CN) and 1 molar equivalent of hydrogen (Hartung, 1982).

In this 2-year dietary study, rats (10/sex/group) were administered food fumigated with HCN. The average daily concentrations were 73 and 183 mg CN/kg diet. From the data reported on food consumption and body weight, daily estimated doses were 4.3 mg and 10.8 mg CN/kg bw. The average food CN concentrations were estimated based on the authors' data for concentration at the beginning and end of each food preparation period and by assuming a first-order rate of loss for the intervening period. There were no treatment related effects on growth rate, no gross signs of toxicity, and no histopathologic lesions.

Studies by Philbrick et al. (1979) showed decreased weight gain and thyroxin levels and myelin degeneration in rats at 30 mg/kg/day CN. Other chronic studies either gave higher effect levels or used the subcutaneous route (Crampton et al., 1979; Lessell, 1971; Hertting et al., 1960). Human data do not provide adequate information from which to derive an RfD because effective dose levels of chronically ingested CN are not documented. Therefore, the study of Howard and Hanzel (1955) provides the highest NOAEL, 10.8 mg/kg/day for CN, and is chosen for the derivation of an RfD for CN of 1.5 mg/day or 0.02 mg/kg/day.

Cyanide is metabolized extensively in the liver, indicating that the only relevant route of administration for quantitative risk assessment in the derivation of an oral RfD is the oral route of administration.

<<< Cyanide, free >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. According to the U.S. EPA (1985), an uncertainty factor of 100 is used to derive the RfD (10 for species extrapolation, 10 for sensitive population).

MF = 5. A modifying factor of 5 is used to account for the apparent tolerance to cyanide when it is ingested with food rather than when it is administered by gavage or by drinking water.

<<< Cyanide, free >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Decreased protein efficiency ratio was produced by dietary cyanide treatment of rats during gestation, lactation and postweaning growth phase in the Tewe and Maner (1981a) experiment: the dose level of cyanide (10.6 mg/kg/day) producing that effect is slightly lower than the currently accepted NOAEL of 10.8 mg/kg/day (U.S. EPA, 1985). Furthermore, Tewe and Maner (1981b) tested sows. Possible effects observed at about 9.45 mg/kg/day were proliferation of glomerular cells of the kidneys and reduced activity of the thyroid glands in the gilts. However, the number of animals in this experiment was very small. A Japanese study (Amo, 1973) indicated that 0.05 mg/kg/day of cyanide obtained from drinking water decreased the fertility rate and survival rate in the F1 generation and produced 100% mortality in the F2 generation in mice. However, these data are not consistent with the body of available literature.

<<< Cyanide, free >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Medium
Data Base: Medium
RfD: Medium

The confidence in the study is medium because adequate records of food consumption and body weight were maintained and animals of both sexes were tested at two doses for 2 years. The data base is rated medium because a small but sufficient number of studies support the chosen study. Medium confidence in the RfD follows. Additional chronic/reproductive studies are needed to support a higher level of confidence in the RfD.

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1984. Health Effects Assessment for Cyanides. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Cyanides. Office of Drinking Water, Washington, DC.

The ODW criteria document and OERR health effects assessment have both had extensive Agency-wide and limited external review.

Agency RfD Work Group Review: 08/05/85

Verification Date: 08/05/85

___I.A.7. EPA CONTACTS (ORAL RfD)

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

Michael L. Dourson / ORD -- (513)569-7544 / FTS 684-7544

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Cyanide, free
CASRN -- 57-12-5

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Cyanide, free
CASRN -- 57-12-5
Last Revised -- 03/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Cyanide, free >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as a human carcinogen.

Basis -- Pertinent data regarding carcinogenicity have not been located in the available literature.

<<< Cyanide, free >>>

___II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Cyanide, free >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

None.

<<< Cyanide, free >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

In vitro studies of genotoxicity have been negative except for a marginally mutagenic response for HCN in Salmonella typhimurium strain TA100 (Kushi et al., 1983). This response was decreased in the presence of rat hepatic homogenates.

----------<<< Cyanide, free >>>----------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

----------<<< Cyanide, free >>>----------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

----------<<< Cyanide, free >>>----------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Cyanide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

<<< Cyanide, free >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1987 Drinking Water Criteria Document on Cyanide has received OHEA review.

Agency Work Group Review: 03/23/88

Verification Date: 03/23/88

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

Nancy Chiu / ODW -- (202)382-7587 / FTS 382-7587

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Cyanide, free
CASRN -- 57-12-5
Last Revised -- 08/01/90

The Office of Drinking Water provides Drinking Water Health Advisories (HAs) as technical guidance for the protection of public health. HAs are not enforceable Federal standards. HAs are concentrations of a substance in drinking water estimated to have negligible deleterious effects in humans, when ingested, for a specified period of time. Exposure to the substance from other media is considered only in the derivation of the lifetime HA. Given the absence of chemical-specific data, the assumed fraction of total intake from drinking water is 20%. The lifetime HA is calculated from the Drinking Water Equivalent Level (DWEL) which, in turn, is based on the Oral Chronic Reference Dose. Lifetime HAs are not derived for compounds which are potentially carcinogenic for humans because of the difference in assumptions concerning toxic threshold for carcinogenic and noncarcinogenic effects. A more detailed description of the assumptions and methods used in the derivation of HAs is provided in Background Document 3 in Service Code 5.

<<< Cyanide, free >>>

___III.A.1. ONE-DAY HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating a One-day HA are not available. It is recommended that a modified DWEL (adjusted for a 10-kg child) of 0.22 mg/L (rounded to 0.2 mg/L) be used as the One-day HA.

<<< Cyanide, free >>>

___III.A.2. TEN-DAY HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating a Ten-day HA are not available. It is recommended that a modified DWEL (adjusted for a 10-kg child) of 0.22 mg/L (rounded to 0.2 mg/L) be used as the Ten-day HA.

<<< Cyanide, free >>>

___III.A.3. LONGER-TERM HEALTH ADVISORY FOR A CHILD

Appropriate data for calculating a Longer-term HA are not available. It is recommended that a modified DWEL (adjusted for a 10-kg child) of 0.22 mg/L (rounded to 0.2 mg/L) be used as the Longer-term HA.

<<< Cyanide, free >>>

___III.A.4. LONGER-TERM HEALTH ADVISORY FOR AN ADULT

Appropriate data for calculating a Longer-term HA are not available. It is recommended that the DWEL of 0.77 mg/L (rounded to 0.8 mg/L) be used as the Longer-term HA for the 70-kg adult.

<<< Cyanide, free >>>

___III.A.5. DRINKING WATER EQUIVALENT LEVEL / LIFETIME HEALTH ADVISORY

DWEL -- 7.7E-1 mg/L

Assumptions -- 2 L/day water consumption for a 70-kg adult

RfD Verification Date = 08/05/85 (see Section I.A. of this file)

Lifetime HA -- 1.54E-1 mg/L

Assumptions -- 20% exposure by drinking water

Principal Study -- Howard and Hanzal, 1955 (This study was used in the derivation of the chronic oral RfD; see Section I.A.2.)

<<< Cyanide, free >>>

___III.A.6. ORGANOLEPTIC PROPERTIES

No data available

<<< Cyanide, free >>>

___III.A.7. ANALYTICAL METHODS FOR DETECTION IN DRINKING WATER

Determination of cyanide is by volumetric titration or colorimetry.

<<< Cyanide, free >>>

___III.A.8. WATER TREATMENT

Treatment technologies that may be practical for reducing cyanide levels in drinking water include oxidation by chlorine or ozone, ion exchange, and reverse osmosis.

<<< Cyanide, free >>>

___III.A.9. DOCUMENTATION AND REVIEW OF HAs

U.S. EPA. 1985. Drinking Water Criteria Document for Cyanide. Office of Drinking Water, Washington, DC.

EPA review of HAs in 1985.

Public review of HAs following notification of availability in October, 1985.

Scientific Advisory Panel review of HAs in January, 1986.

Preparation date of this IRIS summary -- 06/22/87

___III.A.10. EPA CONTACTS

Jennifer Orme / ODW -- (202)382-7586 / FTS 382-7586

Edward V. Ohanian / ODW -- (202)382-7571 / FTS 382-7571

__III.B. OTHER ASSESSMENTS

Substance Name -- Cyanide, free
CASRN -- 57-12-5

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Cyanide, free
CASRN -- 57-12-5
Last Revised -- 08/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections

I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Cyanide, free >>>

__IV.A. CLEAN AIR ACT (CAA)

No data available

---------<<< Cyanide, free >>>---------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

No data available

---------<<< Cyanide, free >>>---------

__IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption: 2E+2 ug/L

Fish Consumption Only: None

Considers technological or economic feasibility? -- NO

Discussion -- This value is the same as the drinking water standard and approximates a safe level assuming consumption of contaminated organisms and water.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Cyanide, free >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 2.2E+1 ug/L
Chronic -- 5.2E+0 ug/L

Marine:

Acute -- 1E+0 ug/L
Chronic -- None

Considers technological or economic feasibility? -- NO

Discussion -- Water quality criteria for the protection of aquatic life are derived from a minimum data base of acute and chronic tests on a variety of aquatic organisms. The data are assumed to be statistically representative and are used to calculate concentrations which will not have significant short- or long-term effects on 95% of the organisms exposed. Recent criteria (1985 and later) contain duration and frequency stipulations: the acute criteria maximum concentration is a 1-hour average and the chronic criteria continuous concentration is a 4-day average which are not to be exceeded more than once every 3 years, on the average (see Stephen et al., 1985). Earlier criteria (1980-1984) contained instantaneous acute and 24-hour average chronic concentrations which were not to be exceeded.

Reference -- 51 FR 8361 (03/11/86)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

----------<<< Cyanide, free >>>----------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

----------<<< Cyanide, free >>>----------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

----------<<< Cyanide, free >>>----------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed (total free cyanide)

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

----------<<< Cyanide, free >>>----------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 10 pounds (Final, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- Cyanides (soluble cyanide salts, not elsewhere specified in Table 302.4 of 40 CFR 302) were placed at RQ level A (10 pounds) on the basis of aquatic toxicity (a 96-Hour Median Threshold Limit between 0.1 and 1 ppm) of the cyanide ion.

Reference -- 50 FR 13456 (04/04/85)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Cyanide, free
CASRN -- 57-12-5

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Cyanide, free
CASRN -- 57-12-5
Last Revised -- 01/01/90

__VI.A. ORAL RfD REFERENCES

Amo, H. 1973. Effects of oral administration of cyanide and heavy metals in long term on breeding and chromosomes analyses of mice. Nagoya shiritsu Diagaku Igakkai Zasshi. 24(1): 48-66.

Crampton, R.F., I.F. Gaunt, R. Harris et al. 1979. Effects of low cobalamin diet and chronic cyanide toxicity. Toxicology. 12: 221-234.

Hartung, R. 1982. Cyanides and nitriles. In: Patty's Industrial Hygiene and Toxicology, 3rd revised ed., Vol. 2c, G.D. Clayton and F.E. Clayton, Ed. John Wiley and Sons, Inc., NY. p. 4845-4900.

Hertting, G., O. Kraupp, E. Schnetz and S. Weeketich. 1960. Untersuchungen uber die Folgen einer chronischen Verabreichung akut toxischer Dosen von Natrimcyanid an Hunden. Acta Pharmacol. Toxicol. 17: 27-43.

Howard, J.W. and R.F. Hanzal. 1955. Chronic toxicity for rats of food treated with hydrogen cyanide. Agric. Food Chem. 3: 325-329.

Lessell, S. 1971. Experimental cyanide optic neuropathy. Arch. Opthalmol.

86(2): 194-204.

Philbrick, D.J., J.B. Hopkins, D.C. Hill, J.C. Alexander and R.G. Thomson. 1979. Effects of prolonged cyanide and thiocyanate feeding in rats. J. Toxicol. Environ. Health. 5: 579-592.

Tewe, O.O. and J.H. Maner. 1981a. Long-term and carry-over effect of dietary inorganic cyanide (KNC) in the life cycle performance and metabolism of rats. Toxicol. Appl. Pharmacol. 58: 1-7.

Tewe, O.O. and J.H. Maner. 1981b. Performance and pathophysiological changes in pregnant pigs fed cassava diets containing different levels of cyanide. Res. Veter. Sci. 30: 147-151.

U.S. EPA. 1984. Health Effects Assessment for Cyanides. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 1985. Drinking Water Criteria Document for Cyanides. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

----------<<< Cyanide, free >>>----------

__VI.B. INHALATION RfD REFERENCES

None

----------<<< Cyanide, free >>>----------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Kushi, A., T. Matsumoto and D. Yoshida. 1983. Mutagen from the gaseous phase of protein pyrolyzate. Agric. Biol. Chem. 47(9): 1979-1982.

U.S. EPA. 1987. Drinking Water Criteria Document for Cyanide. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. External Review Draft.

----------<<< Cyanide, free >>>----------

__VI.D. DRINKING WATER HA REFERENCES

Howard, J.W. and R.F. Hanzal. 1955. Chronic toxicity for rats of food treated with hydrogen cyanide. J. Agric. Food Chem. 3: 325-329.

U.S. EPA. 1985. Drinking Water Criteria Document for Cyanide. Office of Drinking Water, Washington, DC.

SYNONYMS

Substance Name -- Cyanide, free
CASRN -- 57-12-5
Last Revised -- 01/31/87

57-12-5
CARBON NITRIDE ION
CYANIDE
CYANIDE ANION
Cyanide, free
CYANIDE ION
CYANURE
FREE CYANIDE
ISOCYANIDE
RCRA WASTE NUMBER P030

Lead and compounds (inorganic); CASRN 7439-92-1 (05/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Lead and compounds (inorganic)

File On-Line 03/01/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	02/01/91
Inhalation RfC Assessment (I.B.)	no data	
Carcinogenicity Assessment (II.)	on-line	05/01/91
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	07/01/90
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1
Last Revised -- 02/01/91

The Reference Dose (RfD) is based on the assumption that thresholds exist for

certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Lead and compounds (inorganic) >>>

A great deal of information on the health effects of lead has been obtained through decades of medical observation and scientific research. This information has been assessed in the development of air and water quality criteria by the Agency's Office of Health and Environmental Assessment (OHEA) in support of regulatory decision-making by the Office of Air Quality Planning and Standards (OAQPS) and by the Office of Drinking Water (ODW). By comparison to most other environmental toxicants, the degree of uncertainty about the health effects of lead is quite low. It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurdbehavioral development, may occur at blood lead levels so low as to be essentially without a threshold. The Agency's RfD Work Group discussed inorganic lead (and lead compounds) at two meetings (07/08/85 and 07/22/85) and considered it inappropriate to develop an RfD for inorganic lead. For additional information, interested parties are referred to the 1986 Air Quality Criteria for Lead (EPA-600/8-83/028a-dF) and its 1990 Supplement (EPA/600/8-89/049F) or the following Agency scientists:

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

J. Michael Davis / ORD -- (919)541-4162 / FTS 629-4162

Jeff Cohen / ODW -- (202)382-5456 / FTS 382-5456

John Haines / OAQPS -- (919)541-5533 / FTS 629-5533

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1

Not available at this time.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1

Last Revised -- 05/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Lead and compounds (inorganic) >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

___II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- B2; probable human carcinogen

Basis -- Sufficient animal evidence. Ten rat bioassays and one mouse assay have shown statistically significant increases in renal tumors with dietary and subcutaneous exposure to several soluble lead salts. Animal assays provide reproducible results in several laboratories, in multiple rat strains with some evidence of multiple tumor sites. Short term studies show that lead affects gene expression. Human evidence is inadequate.

<<< Lead and compounds (inorganic) >>>

___II.A.2. HUMAN CARCINOGENICITY DATA

Inadequate. There are four epidemiologic studies of occupational cohorts exposed to lead and lead compounds. Two studies (Dingwall-Fordyce and Lane, 1963; Nelson et al., 1982) did not find any association between exposure and cancer mortality. Selevan et al. (1985), in their retrospective cohort mortality study of primary lead smelter workers, found a slight decrease in the total cancer mortality (SMR=95). Apparent excesses were observed for respiratory cancer (SMR=111, obs=41, p>0.05) and kidney cancer (SMR=204, obs=6, p>0.05). Cooper and Gaffey (1975) and Cooper (1985 update) performed a cohort mortality study of battery plant workers and lead smelter workers. They found statistically significant excesses for total cancer mortality (SMR=113, obs=344), stomach cancer (SMR=168, obs=34), and lung cancer (SMR=124, obs=109) in the battery plant workers. Although similar excesses were observed in the smelter workers, they were not statistically significant. Cooper and Gaffey (1975) felt it was possible that individual subjects were monitored primarily on the basis of obvious signs of lead exposure, while others who showed no symptoms of lead poisoning were not monitored.

All of the available studies lacked quantitative exposure information, as well as information on the possible contribution from smoking. All studies also included exposures to other metals such as arsenic, cadmium, and zinc for which no adjustment was done. The cancer excesses observed in the lung and stomach were relatively small (<200). There was no consistency of site among the various studies, and no study showed any dose-response relationship. Thus, the available human evidence is considered to be inadequate to refute or demonstrate any potential carcinogenicity for humans from lead exposure.

<<< Lead and compounds (inorganic) >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

Sufficient. The carcinogenic potential of lead salts (primarily phosphates and acetates) administered via the oral route or by injection has been demonstrated in rats and mice by more than 10 investigators. The most characteristic cancer response is bilateral renal carcinoma. Rats given lead acetate or subacetate orally have developed gliomas, and lead subacetate also produced lung adenomas in mice after i.p. adminstration. Most of these investigations found a carcinogenic response only at the highest dose. The lead compounds tested in animals are almost all soluble salts. Metallic lead, lead oxide and lead tetralkyls have not been tested adequately. Studies of inhalation exposure have not been located in the literature.

Azar et al. (1973) administerd 10, 50, 100, and 500 ppm lead as lead acetate in dietary concentrations to 50 rats/sex/group for 2 years. Control rats (100/sex) received the basal laboratory diet. In a second 2-year feeding study, 20 rats/group were given diets containing 0, 1000, and 2000 ppm lead as lead acetate. No renal tumors were reported in the control groups or in treated animals of either sex receiving 10 to 100 ppm. Male rats fed 500, 1000, and 2000 ppm lead acetate had an increased renal tumor incidence of 5/50, 10/20, and 16/20, while 7/20 females in the 2000-ppm group developed renal tumors.

The Azar et al. (1973) study is limited by the lack of experimental detail. The possibility of environmental contamination from lead in the air or drinking water was not mentioned. The strains of rats used were not specified in the study, but the Health Effects Assessment for Lead (U.S. EPA, 1984) indicates the rats were Wistar strain. The weight gain at 1000 and 2000 ppm was reported to be depressed, but details were not given.

Kasprzak et al. (1985), in investigating the interaction of dietary calcium on lead carcinogenicity, fed 1% lead subacetate (8500 ppm Pb) to male Sprague-Dawley rats in the diet for 79 weeks. Of the rats surviving (29/30) in this treatment group beyond 58 weeks, 44.8% had renal tumors. Four rats had adenocarcinomas; the remainaing nine had adenomas. Bilateral tumors were noted. No renal tumors were noted among the controls.

As part of a study to determine interactions between sodium nitrite, ethyl urea and lead, male Sprague-Dawley rats were given lead acetate in their drinking water for 76 weeks (Koller et al., 1986). The concentration of lead was 2600 ppm. No kidney tumors were detected among the 10 control rats. Thirteen of 16 (81%) lead-treated rats had renal tubular carcinoma; three tumors were detected at 72 weeks and the remainder detected at the termination of the study.

Van Esch and Kroes (1969) fed basic lead acetate at 0, 0.1%, and 1.0% in the diet to 25 Swiss mice/sex/group for 2 years. No renal tumors developed in the control group, but 6/25 male mice of 0.1% basic lead acetate group had renal tumors (adenomas and carcinomas combined). In the 1.0% group, one female had a renal tumor. The authors thought that the low incidence in the 1.0% group was due to early mortality.

Hamsters given lead subacetate at 0.5% and 1% in the diet had no significant renal tumor response (Van Esch and Kroes, 1969).

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Lead acetate induces cell transformation in Syrian hamster embryo cells (DiPaolo et al., 1978) and also enhances the incidence of simian adenovirus induction. Lead oxide showed similar enhanced adenovirus induction (Casto et al., 1979).

Under certain conditions lead compounds are capable of inducing chromosomal aberrations in vivo and in tissue cultures. Grandjean et al. (1983) showed a relationship between SCE and lead exposure in exposed workers. Lead has been shown, in a number of DNA structure and function assays, to affect the molecular processes associated with the regulation of gene expression (U.S. EPA, 1986).

----------<<< Lead and compounds (inorganic) >>>----------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

Quantifying lead's cancer risk involves many uncertainties, some of which may be unique to lead. Age, health, nutritional state, body burden, and exposure duration influence the absorption, release, and excretion of lead. In addition, current knowledge of lead pharmacokinetics indicates that an estimate derived by standard procedures would not truly describe the potential risk. Thus, the Carcinogen Assessment Group recommends that a numerical estimate not be used.

----------<<< Lead and compounds (inorganic) >>>----------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

----------<<< Lead and compounds (inorganic) >>>----------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1984. Health Effects Assessment for Lead. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86/055. NTIS PB85-163996/AS.

U.S. EPA. 1986. Air Quality Criteria Document for Lead. Volumes III, IV. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC, for the Office of Air Quality Planning and Standards. EPA-600/8-83/028dF.

_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1
Last Revised -- 07/01/90

EPA risk assessments may be updated as new data are published and as assessment methodologies evolve. Regulatory actions are frequently not updated at the same time. Compare the dates for the regulatory actions in this section with the verification dates for the risk assessments in sections I and II, as this may explain inconsistencies. Also note that some regulatory actions consider factors not related to health risk, such as technical or economic feasibility. Such considerations are indicated for each action. In addition, not all of the regulatory actions listed in this section involve enforceable federal standards. Please direct any questions you may have concerning these regulatory actions to the U.S. EPA contact listed for that particular action. Users are strongly urged to read the background information on each regulatory action in Background Document 4 in Service Code 5.

<<< Lead and compounds (inorganic) >>>

__IV.A. CLEAN AIR ACT (CAA)

___IV.A.1. NATIONAL AMBIENT AIR QUALITY STANDARD (NAAQS)

Considers technological or economic feasibility? -- No

Discussion -- Under Section 109 of the CAA, EPA has set a primary (health-based) NAAQS for lead of 1.5 ug/cu.m, calendar quarter average not to be exceeded (43 FR 41258, 10/05/78). The secondary (welfare-based) NAAQS is identical to the primary standard. EPA is currently reviewing these standards to determine if changes are warranted.

Reference -- 40 CFR 50.12

U.S. EPA Contact -- Air Quality Management Division / OAQPS / (919)541-5656 / FTS 629-5656

----------<<< Lead and compounds (inorganic) >>>----------

__IV.B. SAFE DRINKING WATER ACT (SDWA)

___IV.B.1. MAXIMUM CONTAMINANT LEVEL GOAL (MCLG) for Drinking Water

Value (status) -- 0.02 mg/L (Proposed, 1985)

Considers technological or economic feasibility? -- NO

Discussion -- Neurological effects of lead in infants and adverse effects associated with blood lead levels of 15 ug/dL are the basis for this MCLG. Using a conversion factor of 6.25 to convert from blood lead concentrations to drinking water lead concentrations and an uncertainty factor of 5, an MCLG of 0.02 mg/L for lead was derived.

Reference -- 50 FR 46936 Part IV (11/13/85)

EPA Contact -- Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

<<< Lead and compounds (inorganic) >>>

___IV.B.2. MAXIMUM CONTAMINANT LEVEL (MCL) for Drinking Water

Value (status) -- 0.05 mg/L (Interim, 1980)

Considers technological or economic feasibility? -- YES

Discussion -- As an interim measure the U.S. EPA is using the value previously derived by the Public Health Service.

Reference -- 45 FR 57332 (08/27/80)

EPA Contact -- Criteria and Standards Division, ODW /
(202)382-7571 / FTS 382-7571; or Drinking Water Hotline / (800)426-4791

----------<<< Lead and compounds (inorganic) >>>----------

___IV.C. CLEAN WATER ACT (CWA)

___IV.C.1. AMBIENT WATER QUALITY CRITERIA, Human Health

Water and Fish Consumption -- 5.0E+1 ug/L

Fish Consumption Only -- None

Considers technological or economic feasibility? -- NO

Discussion -- The criterion was set at the existing drinking water standard in 1980.

Reference -- 45 FR 79318 (11/28/80)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

<<< Lead and compounds (inorganic) >>>

___IV.C.2. AMBIENT WATER QUALITY CRITERIA, Aquatic Organisms

Freshwater:

Acute -- 8.2E+1 ug/L (1-hour average)
Chronic -- 3.2E+0 ug/L (4-day average)

Marine:

Acute -- 1.40E+2 ug/L (1-hour average)
Chronic -- 5.6E+0 ug/L (4-day average)

Considers technological or economic feasibility? -- NO

Discussion -- The toxicity of this compound in freshwater is hardnessdependent. The values given are for a hardness of 100 mg/L $CaCO_3$. For a more complete discussion, see the referenced notice.

Reference -- 50 FR 30784 (07/29/85)

EPA Contact -- Criteria and Standards Division, OWRS
(202)475-7315 / FTS 475-7315

----------<<< Lead and compounds (inorganic) >>>----------

__IV.D. FEDERAL INSECTICIDE, FUNGICIDE, AND RODENTICIDE ACT (FIFRA)

No data available

----------<<< Lead and compounds (inorganic) >>>----------

__IV.E. TOXIC SUBSTANCES CONTROL ACT (TSCA)

No data available

----------<<< Lead and compounds (inorganic) >>>----------

__IV.F. RESOURCE CONSERVATION AND RECOVERY ACT (RCRA)

___IV.F.1. RCRA APPENDIX IX, for Ground Water Monitoring

Status -- Listed

Reference -- 52 FR 25942 (07/09/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

----------<<< Lead and compounds (inorganic) >>>----------

__IV.G. SUPERFUND (CERCLA)

___IV.G.1. REPORTABLE QUANTITY (RQ) for Release into the Environment

Value (status) -- 1 pound (Statutory, 1987)

Considers technological or economic feasibility? -- NO

Discussion -- The statutory 1-pound RQ for lead is retained pending assessment of its potential carcinogenicity and may be adjusted in a future notice of proposed rulemaking when the evaluation of available data is completed. Lead was evaluated for chronic toxicity, but was not ranked for toxicity because of insufficient data.

Reference -- 52 FR 8140 (03/16/87)

EPA Contact -- RCRA/Superfund Hotline
(800)424-9346 / (202)382-3000 / FTS 382-3000

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_V. SUPPLEMENTARY DATA

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1
Last Revised -- 12/01/89

__VI.A. ORAL RfD REFERENCES

None

----------<<< Lead and compounds (inorganic) >>>----------

__VI.B. INHALATION RfD REFERENCES

None

----------<<< Lead and compounds (inorganic) >>>----------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Anderson, E.L., and CAG (Carcinogenic Assessment Group). 1983. Quantitative approaches in use to assess cancer risk. Risk Analysis. 3: 277-295.

Azar, A., H.J. Trochimowicz and M.E. Maxfield. 1973. Review of lead studies in animals carried out at Haskell Laboratory - Two year feeding study and response to hemorrhage study. In: Barth D., A. Berlin, R. Engel, P. Recht and J. Smeets, Ed. Environmental health aspects of lead: Proceedings International Symposium; October 1972; Amsterdam, The Netherlands. Commission of the European Communities, Luxemberg. p. 199-208.

Casto, B.C., J. Meyers and J.A. DiPaolo. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 39: 193-198.

Cooper, W.C. 1985. Mortality among employees of lead battery plants and lead producing plants, 1947-1980. Scand. J. Work Environ. Health. 11: 331-345.

Cooper, W.C. and W.R. Gaffey. 1975. Mortality of lead workers. In: Proceedings of the 1974 Conference on Standards of Occupational Lead Exposure, J.F. Cole, Ed., February, 1974. Washington, DC. J. Occup. Med. 17: 100-107.

Dingwall-Fordyce, I. and R.E. Lane. 1963. A follow-up study of lead workers. Br. J. Ind. Med. 20: 313-315.

DiPaolo, J.A., R.L. Nelson and B.C. Casto. 1978. In vitro neoplastic transformation of Syrian hamster cells by lead acetate and its relevance to environmental carcinogenesis. Br. J. Cancer. 38: 452-455.

Grandjean, P., H.C. Wulf and E. Niebuhr. 1983. Sister chromatid exchange in response to variations in occupational lead exposure. Environ. Res. 32: 199-204.

Kasprzak, K.S., K.L. Hoover and L.A. Poirier. 1985. Effects of dietary calcium acetate on lead subacetate carcinogenicity in kidneys of male Sprague-Dawley rats. Carcinogenesis. 6(2): 279-282.

Koller, L.D., N.I. Kerkvliet and J.H. Exon. 1986. Neoplasia induced in male rats fed lead acetate, ethyl urea and sodium nitrate. Toxicol. Pathol. 13: 50-57.

Nelson, D.J., L. Kiremidjian-Schumacher and G. Stotzky. 1982. Effects of cadmium, lead, and zinc on macrophage-mediated cytotoxicity toward tumor cells. Environ. Res. 28: 154-163.

Selevan, S.G., P.J. Landrigan, F.B. Stern and J.H. Jones. 1985. Mortality of lead smelter workers. Am. J. Epidemiol. 122: 673-683.

Van Esch, G.J. and R. Kroes. 1969. The induction of renal tumors by feeding of basic lead acetate to mice and hamsters. Br. J. Cancer. 23: 265-271.

U.S. EPA. 1984. Health Effects Assessment for Lead. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH, for the Office of Emergency and Remedial Response, Washington, DC. EPA/540/1-86/055. NTIS PB85-163996/AS.

U.S. EPA. 1986. Air Quality Criteria Document for Lead. Volumes III, IV. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC, for the Office of Air Quality Planning and Standards. EPA-600/8-83/028dF.

U.S. EPA. 1987. Preliminary review of the carcinogenic potential of lead associated with oral exposure. Prepared by the Office of Health and Environmental Assessment, Carcinogenic Assessment Group, Washington DC, for the Office of Drinking Water, Office of Solid Waste and the Office of Emergency and Remedial Response (Superfund). OHEA-C-267. Internal Review Draft.

----------<<< Lead and compounds (inorganic) >>>----------

__VI.D. DRINKING WATER HA REFERENCES

None

SYNONYMS

Substance Name -- Lead and compounds (inorganic)
CASRN -- 7439-92-1
Last Revised -- 03/01/88

7439-92-1
Lead
Lead and compounds
plumbum

Mercury (Inorganic); CASRN 7439-97-6 (05/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Mercury (Inorganic)

File On-Line 09/07/88

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	pending	
Inhalation RfC Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	on-line	05/01/91
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	no data	
Supplementary Data (V.)	no data	

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_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6

A risk assessment for this substance/agent is under review by an EPA work group.

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6

A risk assessment for this substance/agent is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6
Last Revised -- 05/01/91

Section II provides information on three aspects of the carcinogenic risk assessment for the agent in question; the U.S. EPA classification, and quantitative estimates of risk from oral exposure and from inhalation exposure. The classification reflects a weight-of-evidence judgment of the likelihood that the agent is a human carcinogen. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. Background Document 2 (Service Code 5) provides details on the rationale and methods used to derive the carcinogenicity values found in IRIS. Users are referred to Section I for information on long-term toxic effects other than carcinogenicity.

<<< Mercury (Inorganic) >>>

__II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

____II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- No human data are available. Animal and supporting data are inadequate.

<<< Mercury (Inorganic) >>>

____II.A.2. HUMAN CARCINOGENICITY DATA

None.

<<< Mercury (Inorganic) >>>

___II.A.3. ANIMAL CARCINOGENICITY DATA

When 39 BD III and BD IV rats were injected i.p. over 2 weeks with 0.1 ml metallic mercury and observed for their lifetimes, sarcomas were seen only in those tissues that had been in direct contact with the metal (Druckrey et al., 1957). No concurrent controls were reported.

<<< Mercury (Inorganic) >>>

___II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Mitsumori et al. (1981) fed groups of 60 male and 60 female SPF ICR mice 0, 15 or 30 ppm methyl mercury chloride in the diet for up to 78 weeks. The majority of the 30 ppm groups died from neurotoxicity by week 26. Histopathology on kidney tissue from all animals surviving after 53 weeks revealed renal tumors in 13/16 males in the 15 ppm group (2 adenomas, 11 adenocarcinomas). One adenoma was detected among 37 controls surviving to week 53 or beyond, and no tumors were seen in either control or exposed females. The possible presence of tumors at other sites was not reported in this preliminary communication.

Methyl mercury hydroxide administered in the diet to Drosophila melanogaster at 5 mg/L induced chromosomal nondisjunction. Methyl and phenyl mercury produced small increases in the rate of point mutations (Ramel, 1972).

The relevance of data from studies of organic mercury to the possible carcinogenicity of inorganic mercury is uncertain.

----------<<< Mercury (Inorganic) >>>----------

__II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

Not available.

----------<<< Mercury (Inorganic) >>>----------

__II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

Not available.

----------<<< Mercury (Inorganic) >>>----------

__II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

___II.D.1. EPA DOCUMENTATION

U.S. EPA. 1987. Drinking Water Criteria Document for Mercury. Prepared for the Office of Drinking Water, Washington, DC. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. ECAO-CIN-025, February, 1987.

<<< Mercury (Inorganic) >>>

___II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

The 1987 Drinking Water Criteria Document for Mercury has received Agency and external review.

Agency Work Group Review: 01/13/88

Verification Date: 01/13/88

___II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

W. Bruce Peirano / ORD -- (513)569-7540 / FTS 684-7540

Krishan Khanna / ODW -- (202)382-7588 / FTS 382-7588

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_III. HEALTH HAZARD ASSESSMENTS FOR VARIED EXPOSURE DURATIONS

__III.A. DRINKING WATER HEALTH ADVISORIES

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6

Not available at this time.

__III.B. OTHER ASSESSMENTS

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6

Content to be determined.

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_IV. U.S. EPA REGULATORY ACTIONS

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6

Not available at this time.

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_V. SUPPLEMENTARY DATA

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6

Not available at this time.

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_VI. BIBLIOGRAPHY

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6
Last Revised -- 09/01/89

__VI.A. ORAL RfD REFERENCES

None

----------<<< Mercury (Inorganic) >>>----------

__VI.B. INHALATION RfD REFERENCES

None

----------<<< Mercury (Inorganic) >>>----------

__VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Druckrey, H., H. Hamperl and D. Schmahl. 1957. Carcinogenic action of metallic mercury after intraperitoneal administration in rats. Z. Krebsforsch. 61: 511-519.

Mitsumori, K., K. Maita, T. Saito, S. Tsuda and Y. Shikasu. 1981. Carcinogenicity of methylmercury chloride in ICR mice: Preliminary note on renal carcinogens. Cancer Lett. 12: 305-310.

Ramel, C. 1972. Genetic effects. In: Mercury in the Environment -- An Epidemiological and Toxicological Appraisal, L. Friberg and J. Vostal, Ed. CRC Press, Cleveland, OH. p. 169-181.

U.S. EPA. 1987. Drinking Water Criteria Document for Mercury. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC.

----------<<< Mercury (Inorganic) >>>----------

__VI.D. DRINKING WATER HA REFERENCES

None

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SYNONYMS

Substance Name -- Mercury (Inorganic)
CASRN -- 7439-97-6
Last Revised -- 09/07/88

7439-97-6
hydragyrum
Mercury

Nickel, soluble salts; CASRN 7440-02-0 (06/01/91)

Health risk assessment information on a chemical is included in IRIS only after a comprehensive review of chronic toxicity data by work groups composed of U.S. EPA scientists from several Program Offices. The summaries presented in Sections I and II represent a consensus reached in the review process. The other sections contain U.S. EPA information which is specific to a particular EPA program and has been subject to review procedures prescribed by that Program Office. The regulatory actions in Section IV may not be based on the most current risk assessment, or may be based on a current, but unreviewed, risk assessment, and may take into account factors other than health effects (e.g., treatment technology). When considering the use of regulatory action data for a particular situation, note the date of the regulatory action, the date of the most recent risk assessment relating to that action, and whether technological factors were considered. Background information and explanations of the methods used to derive the values given in IRIS are provided in the five Background Documents in Service Code 5, which correspond to Sections I through V of the chemical files.

STATUS OF DATA FOR Nickel, soluble salts

File On-Line 09/30/87

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	06/01/90
Inhalation RfC Assessment (I.B.)	pending	
Carcinogenicity Assessment (II.)	message	
Drinking Water Health Advisories (III.A.)	no data	
U.S. EPA Regulatory Actions (IV.)	on-line	06/01/90
Supplementary Data (V.)	on-line	09/30/87

_I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

__I.A. REFERENCE DOSE FOR CHRONIC ORAL EXPOSURE (RfD)

Substance Name -- Nickel, soluble salts
CASRN -- 7440-02-0
Last Revised -- 06/01/90

The Reference Dose (RfD) is based on the assumption that thresholds exist for

certain toxic effects such as cellular necrosis, but may not exist for other toxic effects such as carcinogenicity. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to Background Document 1 in Service Code 5 for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of compounds which are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file when a review of that evaluation is completed.

<<< Nickel, soluble salts >>>

NOTE: The Oral RfD for nickel (soluble salts) may change in the near future pending the outcome of a further review now being conducted by the Oral RfD Work Group.

___I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
Decreased body and organ weights	NOAEL: 100 ppm diet (5 mg/kg/day)	100	3	2E-2 mg/kg/day
Chronic Rat Feeding Study	LOAEL: 1000 ppm diet (50 mg/kg/day)			
Ambrose et al., 1976				

*Conversion Factors: 1 ppm = 0.05 mg/kg/day (assumed rat food consumption)

<<< Nickel, soluble salts >>>

___I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Ambrose, A.M., D.S. Larson, J.R. Borzelleca and G.R. Hennigar, Jr. 1976. Long-term toxicologic assessment of nickel in rats and dogs. J. Food Sci. Technol. 13: 181-187.

Ambrose et al. (1976) reported the results of a 2-year feeding study using rats given nickel sulfate hexahydrate in concentrations of 0, 100, 1000 or 2500 ppm as nickel (Ni) (estimated as 0, 5, 50, and 125 mg Ni/kg bw) in the diet. Body weights in the high-dose male and female rats were significantly decreased compared with controls. Body weight was also reduced at 1000 ppm; this reduction was significant for females at week 6 and from week 26 through 104, whereas males showed body weight reductions only at 52 weeks. Groups of female rats on the 1000 or 2500 ppm nickel diets (50 and 125 mg Ni/kg bw) had significantly higher heart-to-body weight ratios and lower liver-to-body weight ratios than controls. No significant effects were reported at 100 ppm (5 mg Ni/kg bw). The dose of 1000 ppm (50 mg Ni/kg bw) represents a LOAEL for this study, while the 100 ppm (5 mg Ni/kg bw) dose is a NOAEL. In this study, 2-year survival was poor, particularly in control rats of both sexes (death: 44/50); this raised some concern about the interpretation of the results of this study.

A subchronic study conducted by American Biogenics Corp. (U.S. EPA, 1986) also found 5 mg/kg/day to be a NOAEL, which supports the Ambrose et al. (1976)

chronic NOAEL of 5 mg/kg/day. U.S. EPA (1986) reported that the 90-day study with nickel chloride in water (0, 5, 35, and 100 mg/kg/day) was administered by gavage to both male and female CD rats (30 animals/sex/group). The data generated in this study included clinical pathology, ophthalmologic evaluations, serum biochemistry, body and organ weight changes, and histopathologic evaluations of selected organs (heart, kidney, liver). The body weight and food consumption values were consistently lower than controls for the 35 and 100 mg/kg/day dosed males. Female rats in both high-dose groups had lower body weights than controls, but food consumption was unaffected by the chemical. Clinical signs of toxicity, such as lethargy, ataxia, irregular breathing, cool body temperature, salivation, and discolored extremities, were seen primarily in the 100 mg/kg/day group; these signs were less severe in the 35 mg/kg/day group. The 5 mg/kg/day group did not show any significant clinical signs of toxicity. There was 100% mortality in the high-dose group; 6/30 males and 8/30 females died in the mid-dose group (35 mg/kg/day). Histopatho- logic evaluation indicated that the deaths of 3/6 males and 5/8 females in the mid-dose group were due to gavage errors. At sacrifice, kidney, liver, and spleen weights for males treated at the 35 mg/kg/day dose level and right kidney weights for females treated at the 35 mg/kg/day dose level were significantly lower than controls. Based on the results obtained in this study, the 5 mg/kg/day nickel dose was a NOAEL, whereas the 35 mg/kg/day was a LOAEL for decreased body and organ weights.

<<< Nickel, soluble salts >>>

___I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF = 100. An uncertainty factor of 100 is used: 10 for interspecies extrapolation and 10 to protect sensitive populations. The nickel dietary study by Ambrose et al. (1976) identifying a NOAEL of 100 ppm (5 mg/kg/day) is supported by the subchronic gavage study in water (U.S. EPA, 1986), which indicated the same NOAEL (5 mg/kg/day). The uncertainty factor of 100 is therefore appropriate, since two studies support the NOAEL of 5 mg/kg/day.

MF = 3. A modifying factor of 3 is used because of inadequacies in the reproductive studies (RTI, 1987; Ambrose et al., 1976, see Additional Comments section). During the gestation and postnatal development of F1b litters in the RTI (1987) study, temperatures were about 10F higher than normal at certain times, which makes evaluation of this part of the reproductive study impossible. In the Ambrose et al. (1976) study there were some statistical design limitations, such as small sample size and use of pups rather than litters as the unit for comparison.

<<< Nickel, soluble salts >>>

___I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

Ambrose et al. (1976) also reported reproductive toxicity of nickel, but the study had some statistical design limitations, such as small sample size and use of pups rather than litters as the unit for comparison. Furthermore, the results were equivocal and did not clearly define a NOAEL or LOAEL. The fact that nickel was administered in a laboratory chow diet containing milk powder, rather than in drinking water, in this study caused problems in quantification of nickel exposure when applying these data to drinking water situations.

In a 2-generation study (RTI, 1987), nickel chloride was administered in drinking water to male and female CD rats (30/sex/group) at dose levels of 0, 50, 250, and 500 ppm (0, 7.3, 30.8, and 51.6 mg/kg/day, estimated) for 90 days prior to breeding (10 rats/sex/group comprised a satellite subchronic nonbreeder group). At the 500 ppm dose level there was a significant decrease in the P-zero maternal body weights, along with absolute and relative liver weights. Thus, 250 ppm (30.8 mg/kg/day) was a NOAEL for P-zero breeders. Histopathology was performed for liver, kidney, lungs, heart, pituitary, adrenals, and reproductive organs to make this assessment. This NOAEL is higher than the NOAEL derived from the chronic Ambrose et al. (1976) and subchronic gavage (U.S. EPA, 1986) assays.

The number of live pups/litter was significantly decreased, pup mortality was significantly increased, and average pup body weight was significantly decreased in comparison with controls for the F1a generation (postnatal days 1-4) at the 500 ppm dose level (RTI, 1987). Similar effects were seen with F1b litters of P-zero dams exposed to 500 ppm nickel. In the 50 and 250 ppm dose group, increased pup mortality and decreased live litter size were observed in the F1b litters. However, these effects seen with F1b litters are questionable because the room temperature tended to be 10F higher than normal at certain times (gestation-postnatal days) along with much lower levels of humidity. As evidenced in the literature, temperatures that are 10F above normal during fetal development cause adverse effects (Edwards, 1986). Therefore, the above results seen at the 50 and 250 dose levels cannot be considered as genuine adverse effects.

F1b males and females of the RTI (1987) study were randomly mated on postnatal day 70 and their offspring (F2a and F2b) were evaluated through postnatal day 21. This phase included teratologic evaluations of F2b fetuses. Evaluation of the data indicated that the 500 ppm dose caused significant body weight depression of both mothers and pups, and increased neonatal mortality during the postnatal development period. The intermediate dose, 250 ppm nickel, produced transient depression of maternal weight gain and water intake during gestation of the F2b litters. The 50 ppm nickel exposure caused a significant increase in short ribs (11%). However, since this effect was not seen in both of the higher dose groups, the reported incidence of short ribs in the 50 ppm group is not considered to be of biological significance.

Schroeder and Mitchener (1971) conducted a 3-generation study in which five mating pairs of rats were provided drinking water containing 5 mg Ni/L (estimated as 0.43 mg/kg bw). Results of this study indicated significant increases in neonatal mortality and number of runts born to exposed rats compared with controls. The major weakness of this study, however, is that the end result is based on a total of five matings. The matings were not randomized and the males were not rotated. The Schroeder and Mitchener (1971) study was conducted in an environmentally controlled facility where rats had access to food and water containing minimal levels of essential trace metals. Because of the interaction of nickel with other trace metals, the restricted exposure to trace metals (chromium was estimated as inadequate) may have contributed to the toxicity of nickel.

<<< Nickel, soluble salts >>>

___I.A.5. CONFIDENCE IN THE ORAL RfD

Study: Low
Data Base: Medium
RfD: Medium

The chronic study (Ambrose et al., 1976) was properly designed and provided adequate toxicologic endpoints; however, there was high mortality in the controls (44/50). Therefore, a low confidence is recommended for the study. The data base provided adequate supporting subchronic studies, one by gavage and the other in drinking water [P-zero animals of the RTI (1986) subchronic study]. A medium confidence level in the data base is recommended because there are inadequacies in the remaining reproductive study data. The RfD is adequately supported by the oral subchronic and reproductive studies, and until additional reproductive studies are available a medium confidence in the RfD is recommended.

<<< Nickel, soluble salts >>>

___I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

U.S. EPA. 1983. Health Assessment Document for Nickel. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Research Triangle Park, NC. External Review Draft.

U.S. EPA. 1985. Drinking Water Criteria Document for Nickel - Quantification of Toxicological Effects Chapter Only. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Drinking Water, Washington, DC. EPA 600/x-84-193-1.

Extensive Agency-wide Review, 1987

Agency RfD Work Group Review: 04/16/87, 05/20/87, 07/16/87

Verification Date: 07/16/87

___I.A.7. EPA CONTACTS (ORAL RfD)

Harlal Choudhury / ORD -- (513)569-7536 / FTS 684-7536

Christopher T. DeRosa / ORD -- (513)569-7534 / FTS 684-7534

__I.B. REFERENCE CONCENTRATION FOR CHRONIC INHALATION EXPOSURE (RfC)

Substance Name -- Nickel, soluble salts
CASRN -- 7440-02-0

A risk assessment for this substance/agent is under review by an EPA work group.

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_II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Nickel, soluble salts
CASRN --- 7440-02-0

The U.S. EPA has not evaluated soluble salts of nickel, as a class of compounds, for potential human carcinogenicity. However, nickel refinery dust